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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,879	10/09/2003	William C. Olson	2048/61009-A/JPW/MAF	7724

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EXAMINER	
CHEN, STACY BROWN	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
09/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/681,879	**Applicant(s)** OLSON ET AL.	
	Examiner Stacy B. Chen	**Art Unit** 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10-13,42-45 and 47-52* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1,10-13,42-45 and 47-52* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *09 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 7, 2007 has been entered. Claims 1, 10-13, 42-45 and 47-52 are pending and under examination. Note that the claim listing filed August 7, 2007 has two claims notated as "51". The Office considers the second claim 51 to be claim 52, according to 37 C.F.R. 1.126. A corrected claim listing is required in the next amendment.

Response to Amendment

2. The rejection of claim 46 under 35 U.S.C. 101 as claiming the same invention as that of claim 3 of prior U.S. Patent No. 6,692,745 B2, is moot in view of the cancellation of claim 46.

Claims Summary and Interpretation

3. The claims as amended are drawn to a composition comprising:

- A monoclonal antibody or a portion thereof that retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell; the antibody is either human, humanized, or chimeric, and it binds either gp120 or CD4; and,

- T-20 (SEQ ID NO: 1), which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate.

The relative mass ratio of the compounds in the admixture ranges from about 100:1 to about 1:100, wherein the composition inhibits HIV-1 infection of the CD4+ cell. Also claimed are methods of inhibiting HIV-1 infection of a CD4+ cells by administering the claimed composition.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 10-13, 42-45 and 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allaway *et al.* (5,817,767, "Allaway") in view of Bolognesi *et al.* (5,464,933, "Bolognesi"). The claims are summarized above, and the rejection is of record. To summarize the rejection, Allaway discloses compositions comprising CD4-based immunoconjugates and antibodies specific for gp120 (see abstract) in a ratio of between about 0.01 and about 100 (see col. 4, lines 33-43); the antibodies are human, murine or humanized murine anti-gp120 and anti-gp41 monoclonal antibodies (see col. 14, lines 44-53). Allaway's composition is administered to a subject to reduce the rate of spread of HIV-1 infection in a subject (see col. 5, lines 39-59). Regarding the Fab fragment, Allaway is silent on the Fab portion of the antibody as a compound that interferes with gp120 binding to CD4. However, it is well known in the art that the Fab fragment (containing at least a variable region and a CDR) is the portion that binds epitopes because it contains the variable regions. Allaway fails to teach a peptide that binds the gp41 fusion intermediate as instantly claimed. However, Bolognesi discloses that DP-178 (T-20, SEQ ID NO: 1) exhibits potent anti-HIV transmission activity (see abstract and col. 5, lines 19-29). One of ordinary skill in the art would have been motivated to use the peptides of Bolognesi in Allaway's method because Allaway teaches the use of agents that bind gp41. One would have had a reasonable expectation of success that the use of Bolognesi's peptides in lieu of Allaway's agent would have interfered with gp41 fusion because both agents (the monoclonal antibody of Allaway and the T-20 peptide of Bolognesi) bind gp41, whether in the original state or in the fusion intermediate state. The Office recognizes that Allaway does not specifically mention the use of agents that bind epitopes of gp41 fusion intermediates, however, Allaway does teach the use of agents that bind gp41 generally.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant maintains the argument that Allaway's anti-gp41 antibody binds gp41 prior to a conformation change that takes place when gp41 and CD4 bind. Applicant argues that the T-20 peptides binds gp41 after gp41 binds to CD4, during an intermediate fusion state, thus Allaway's molecule and Bolognesi's molecule bind to distinct epitopes on gp41. Applicant notes that Allaway does not appreciate the existence of any transiently exposed epitopes of gp41 during the intermediate fusion state, nor the targeting of gp41 during the intermediate fusion state. Applicant also argues that Allaway's antibody and Bolognesi's peptide are structurally distinct molecules. Applicant concludes that Allaway's antibody and Bolognesi's peptide are not functional equivalents.

- In response to Applicant's arguments, the Office recognizes that the structure of an antibody and a peptide are distinct. However, the antibody and the peptide serve the same purpose: inhibit the fusion of gp41 and CD4. Note that Allaway's disclosure, as a whole with regard to blocking fusion of gp41 and CD4, is concerned with blocking fusion generally. Allaway does not set forth a method that is purely limited to blocking fusion at a particular epitope, rather, the goal of the method is to block fusion. (Note that Allaway's disclosure of the 2F5 antibody is just an example, not a limiting definition of the epitope to which the antibodies of the method must bind.) Since this larger goal of blocking fusion can be accomplished with another molecule, such as the T-20 peptide, the Office considers the antibody and the peptide to be functional equivalents. Further, the function of the T-20 peptide is expected to yield a predictable result, since Bolognesi establishes that the T-20 peptide blocks fusion of gp41 and CD4. The simple substitution of one known element for another to obtain a predictable result is an acceptable rationale for arriving at the conclusion of obviousness.

- Applicant argues that there is unexpected superiority attributable to the two peptidyl compounds recited in Applicant's claims relative to the two peptidyl compounds in Allaway. Applicants points to page 26, lines 8-10, which explains that the degree of synergy was quantified using the Combination Index (CI) method, wherein a CI value greater than 1 indicates antagonism, and a CI equal to 1 indicates a purely additive effect. A CI less than 1 indicates a synergistic effect. Applicant notes that the average CI values in Figure 2 for 95%, 90% and 75% inhibition are 0.31, 0.36 and 0.47, respectively. In contrast, Applicant notes that the average CI values for the same percentages of inhibition disclosed in Allaway (col. 17, Table 2) are 0.50, 0.56 and 0.70, respectively. The Table is reproduced below for convenience.

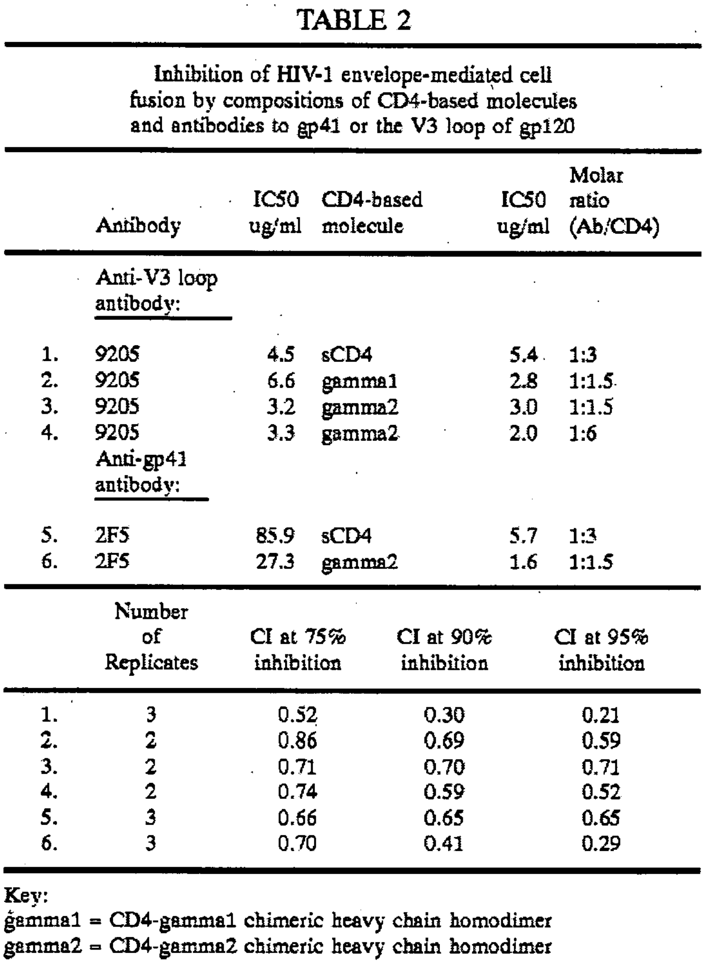

TABLE 2

Inhibition of HIV-1 envelope-mediated cell fusion by compositions of CD4-based molecules and antibodies to gp41 or the V3 loop of gp120

	Antibody	IC50 ug/ml	CD4-based molecule	IC50 ug/ml	Molar ratio (Ab/CD4)
	Anti-V3 loop antibody:				
1.	9205	4.5	sCD4	5.4	1:3
2.	9205	6.6	gamma1	2.8	1:1.5
3.	9205	3.2	gamma2	3.0	1:1.5
4.	9205	3.3	gamma2	2.0	1:6
	Anti-gp41 antibody:				
5.	2F5	85.9	sCD4	5.7	1:3
6.	2F5	27.3	gamma2	1.6	1:1.5

	Number of Replicates	CI at 75% inhibition	CI at 90% inhibition	CI at 95% inhibition
1.	3	0.52	0.30	0.21
2.	2	0.86	0.69	0.59
3.	2	0.71	0.70	0.71
4.	2	0.74	0.59	0.52
5.	3	0.66	0.65	0.65
6.	3	0.70	0.41	0.29

Key:
gamma1 = CD4-gamma1 chimeric heavy chain homodimer
gamma2 = CD4-gamma2 chimeric heavy chain homodimer

- In response to these arguments, the average values that Applicant has calculated are not significantly greater than the results of Allaway's combination. If one were to examine the individual values obtained prior to averaging the values, one

> would observe that there are overlapping values between the two results sets. Applicant's conclusion of unexpected results appears to be based on the values obtained by averaging the CI values, while one observing the individual CI values would note that there is overlap between the two, and thus the results are not significantly greater than those obtained in Allaway's method. Further, Allaway teaches synergism when combining the inhibition of gp120 and the inhibition of gp41 (col. 4, lines 20-30). Although Allaway uses a different molecule to inhibit gp41, the synergism comes from the combination of targeting gp120 and gp41. This is the same combination that Applicant is using and claiming as exhibiting synergism. Even if the asserted synergistic results were to be deemed significantly greater than Allaway's results, the meaning of such a conclusion merely shows that the *specific* combination of T-20 and CD4-IgG2 results in synergism greater than expected.

Therefore, in view of Allaway's disclosure of the basic mechanism of the instant invention, and Bolognesi's disclosure of a functional equivalent of Allaway's antibody to bind gp41, the invention as broadly claimed, would have been obvious. Allaway's disclosure of synergism as a result of combining a molecule that binds gp120 with a molecule that binds gp41 renders the instant invention obvious.

5. Claims 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (US Patent 5,691,976) in view of Bolognesi *et al.* (5,464,933, "Bolognesi"). The claims require that the monoclonal antibody or portion thereof bind to CD4 of a CD4+ cell and thus retard

attachment of gp120 to CD4. Wang discloses monoclonal anti-CD4 antibodies and antibody homologs (fragments, including Fab fragments) that are humanized or chimeric (col. 11, lines 36-53). The antibodies bind to CD4 and retard attachment (block binding) of gp120 to surface CD4 (col. 12, lines 41-44). Also disclosed are methods of administering the antibodies to a subject in combination with other therapeutics for the treatment of HIV infection (col. 19, lines 40-67). Wang does not specifically teach the use of T-20 in combination with the anti-CD4 antibodies. However, Bolognesi discloses that DP-178 (T-20, SEQ ID NO: 1) exhibits potent anti-HIV transmission activity (see abstract and col. 5, lines 19-29). It would have been obvious to combine the anti-CD4 antibody and the T-20 peptide of Bolognesi into a combination therapy composition and method of treatment. One would have been motivated to do make this combination because it would result in a composition that targets multiple aspects of HIV infection, thus improving the treatment efficacy. As is commonly recognized in the art, evidenced by Wang's teaching that the antibodies may be used in combination with other HIV therapeutics, combination therapies for HIV infection are routine.

With regard to the relative mass ratios of Wang's antibody to Bolognesi's peptide, it is routine in the art and would have been well within the ability of the ordinary artisan to determine the ratio of compounds that would exhibit the desired effect of inhibiting HIV infection in a cell. Therefore, the invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

6. Claims 1, 10-13, 42-45 and 47-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,692,745 B2, for reasons of record. Applicant indicated that they may consider filing a terminal disclaimer later in prosecution should allowable claims be indicated.

Conclusion

7. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 9-19-2007
Primary Examiner, TC1600